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### Antacids, sucralfate and bismuth salts for functional dyspepsia

Abdar Esfahani, Meisam; Ahmadi, Najme; Keikha, Mojtaba; Adibi, Peyman; Sharma, Neel; Sharma, Neel; Moayyedi, Paul

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## **Antacids, sucralfate and bismuth salts for functional dyspepsia (Protocol)**

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# Antacids, sucralfate and bismuth salts for functional dyspepsia

Meisam Abdar Esfahani<sup>1</sup>, Najme Ahmadi<sup>1</sup>, Mojtaba Keikha<sup>2</sup>, Peyman Adibi<sup>3</sup>, Neel Sharma<sup>4</sup>, Paul Moayyedi<sup>5</sup>

<sup>1</sup>Isfahan Student Research Committee, Isfahan University of Medical Sciences, Isfahan, Iran. <sup>2</sup>Department of Epidemiology, Shahrood University of Medical Sciences, Shahrood, Iran. <sup>3</sup>Isfahan University of Medical Sciences, Isfahan, Iran. <sup>4</sup>Gastroenterology and Hepatology, NUHS, Singapore, Singapore. <sup>5</sup>Department of Medicine, Division of Gastroenterology, McMaster University, Hamilton, Canada

Contact address: Meisam Abdar Esfahani, Isfahan Student Research Committee, Isfahan University of Medical Sciences, Hezarjerib St, Isfahan, Iran. [igisr@mui.ac.ir](mailto:igisr@mui.ac.ir), [Csr.ugi@gmail.com](mailto:Csr.ugi@gmail.com).

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## ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

### Primary

Effectiveness of antacids, sucralfate and bismuth salts in reducing overall functional dyspepsia symptoms in dyspeptic people.

### Secondary

1. Quality of life
2. Individual dyspepsia symptom change
3. Adverse events and complications

## BACKGROUND

### Description of the condition

Functional (or non-ulcer) dyspepsia (FD) is characterized by the presence of one or more of the following items: epigastric (over the stomach) pain or burning, postprandial (occurring after a meal) epigastric fullness sensation, early satiation or complaint of inability to finish a regular meal, with no anatomical abnormality (detected by gastroscopy, an examination of the upper digestive tract using a long, thin, flexible tube containing a camera and a light

to view the lining of these organs) or routinely detectable motility (contraction of the muscles) disorder to explain the symptoms. In reference to the Rome III criteria, these items should be present for the last three months with symptom onset at least six months before diagnosis (Kourikou 2015). The prevalence of FD differs between 5% to 40%, depending on geographical area and variation in definition criteria (Amini 2012; Lacy 2013; Mahadeva 2016).

Several factors have been demonstrated as the pathophysiologic (the abnormal physical states that accompany a disease) aspects of FD such as alterations in gastric acid secretion, gastroduodenal dysmotility (relating to the stomach and intestines, impaired mus-

cle), visceral hypersensitivity (excessive pain sensitivity in internal organs) *Helicobacter pylori* infection, genetics and psychological elements (Moayyedi 2011; Overland 2014).

Functional dyspepsia has been associated with several genetic polymorphisms (occurring in several different forms) (G-protein B3, serotonin transporter promoter, interleukin-17F, migration inhibitory factor, cholecystocynine-1; intron 1, cyclooxygenase-1, catechol-O-methyl-transferase, transient receptor potential vanilloid1 receptor, regulated upon activation normal T cell expressed and secreted, p22 PHOX, Toll like receptor 2, SCN10 A, CD14 and adrenoreceptors) that play a role in visceral hypersensitivity and other upper abdominal symptoms (Kourikou 2015; Overland 2014). Moreover, history of acute infectious gastroenteritis is another factor that suggested patients with FD are slower, or unable, to terminate the inflammatory response (Overland 2014).

Anxiety, chronic tension, hostility, and hypochondriasis are more common in patients with FD compared with the normal population (Hallissey 1987). Fifty per cent of Europeans and North Americans and two-thirds of patients who had consulted a physician were receiving medication for their dyspepsia (Overland 2014). Also, due to burdensome symptoms, more than 30% of patients miss work or school hours (Mahadeva 2016; Overland 2014). The clinical management of functional dyspepsia, in view of the unknown cause and poorly understood pathophysiology, is still controversial.

## Description of the intervention

Since various pathophysiological factors for FD seem to interact, several treatment modalities including pharmacological or nonpharmacological have been suggested in its management (Talley 1991; Talley 1995). Pharmacological treatment includes H<sub>2</sub> -receptor antagonists (Bekhti 1979; Holtmann 2002; Talley 1998; Van Outryve 1993), proton pump inhibitors (McColl 1998; Wong 2002), *Helicobacter pylori* eradication therapy (Blum 1998; Froehlich 2001; Hamilton 2000; Talley 1998; Talley 1999), and even antidepressants or psychological interventions (Bolling-Sternevald 2003; Calvert 2002).

Other treatment modalities may also be important. Bismuth salts were more effective than placebo for the treatment of functional dyspepsia (Moayyedi 2006). The majority of studies suggested that bismuth was efficacious to assess *H. pylori* eradication in functional dyspepsia (Moayyedi 2006; Talley 2005). In view of the fact that bismuth salts have been associated with neurotoxicity (damage to the brain and nervous system by a poisonous substance) when used long term, this prescription was not recommended as a first-line therapy. The outcomes of treatment with sucralfate for FD are also controversial. Some trials demonstrated that sucralfate improved FD symptoms, but it seems that there is little evidence of comparisons of placebo with sucralfate (Moayyedi 2006; Talley 2005). Evaluation for the efficacy of antacids was done in small patient cohorts, but no evidence was identified that compared

antacids with placebo for FD treatment. Antacids are routinely used, but there is a lack of strong evidence for its effectiveness (Overland 2014).

## How the intervention might work

Antacids reduce acid-related symptoms such as abdominal pain (especially fasting pain) and burning sensations (Chen 2013). Antacids also may increase angiogenesis (the formation of different blood vessels), they bind bile acid and also inhibit peptic (relating to digestion) activity. Also, the heavy metals aluminum and magnesium hydroxide decreased peptic activity but did not eradicate *H. pylori*.

Antacids containing magnesium cause diarrhoea and hypermagnesaemia; the latter only becomes important in patients with renal insufficiency. Amounts of calcium and alkali, particularly calcium carbonate, can result in hypercalcaemia, alkalosis, and acute or chronic renal injury, known as the milk-alkali syndrome (Orwoll 1982). Significant aluminium retention occurs in patients with renal failure and may lead to neurotoxicity and anaemia following prolonged treatment with aluminium hydroxide (Shields 1978a). Sucralfate improves acid-related symptoms and dysmotility-like symptoms in FD. Also sucralfate stimulates angiogenesis and the formation of granulation tissue (material formed in repair of wounds of soft tissue), due to growth factor binding. Moreover, sucralfate suppresses *H. pylori* and inhibits acid secretion and decreases symptoms in some patients. Adverse effects of sucralfate are few (Soll 1991). Constipation may occur in 2% patients and, similar to antacids, aluminium retention in patients with renal failure is possible.

Bismuth can suppress *H. pylori* and this may indicate its appropriateness for FD. Also bismuth inhibits peptic activity, but not pepsin release or gastric acid secretion.

## Why it is important to do this review

During the last decade, several published systematic reviews and meta-analyses have recommended different treatments for functional dyspepsia such as antacids, sucralfate and bismuth salts (Hansen 1998; Moayyedi 2006; Moayyedi 2011; Suzuki 2011). Since then, several RCTs were published that investigated the efficacy of these drugs, but no systematic reviews assessed these studies and a previous Cochrane systematic review has been withdrawn (Moayyedi 2011).

Antacid, sucralfate and bismuth could decrease the stimulating factors that may make positive effects on FD. Also antacids, sucralfate and bismuth salts are available without prescription, and are inexpensive. Since functional dyspepsia is a recurrent disorder, and these drugs are widely available, they appear to be easy to use remedy options. Evidence for the real efficacy of these drugs in

functional dyspepsia will help physicians to understand when to prescribe them or avoid their use altogether.

## OBJECTIVES

### Primary

Effectiveness of antacids, sucralfate and bismuth salts in reducing overall functional dyspepsia symptoms in dyspeptic people.

### Secondary

1. Quality of life
2. Individual dyspepsia symptom change
3. Adverse events and complications

## METHODS

### Criteria for considering studies for this review

#### Types of studies

All experimental or interventional studies, without any limitation in type and details, that studied the effectiveness of three classes of drugs (antacids, sucralfate and bismuth salts) in the improvement of either individual or global dyspepsia.

#### Types of participants

We will include all participants over 18 years, of both genders, with a diagnosis of functional dyspepsia (functional or non-ulcer dyspepsia) according to any well-defined criteria (such as Rome I, II, III, IV or Lancet Working Group).

Studies that included other gastrointestinal diseases, such as peptic ulcer, organic dyspepsia and reflux disease will be excluded.

This may be confirmed by checking if upper gastrointestinal endoscopy or any other diagnostic modality was performed in participant recruitment for the study.

If a study included populations with different conditions, we will only include participants with functional dyspepsia.

Participants in the trials that did not have any positive findings at endoscopy or barium study, symptoms of hiatus hernia, less than five gastric erosions or mild duodenitis will be included. We will include all participants, naive or with a history of treatment of FD and we will include all types of participant that were recruited in

studies such as participants in primary care, secondary or tertiary care, or convenience sample.

#### Types of interventions

We will include trials comparing oral administration of any dose of any available drug (antacids, sucralfate and bismuth salts) with placebo.

#### Types of outcome measures

Outcomes in FD may be measured by an ordinal or dichotomous (improved/not improved) scale. In ordinal measures, such as the five-point Likert scale, we will assume that they are continuous measures or variables and, for interpretation, we will use standardized mean differences.

In ordinal scales with a variety of answers, we will assume that scores above the mean are improved and those lower than the mean are not improved.

#### Primary outcomes

Effectiveness of the three classes of drugs (antacids, sucralfate and bismuth salts) in reducing overall functional dyspepsia symptoms.

#### Secondary outcomes

1. Quality of life score increment
2. Individual dyspepsia symptoms score reduction or disappearance
3. Adverse events

#### Time (duration of therapy)

We will consider interventions of at least four weeks duration (studies with outcome assessment carried out at less than four weeks will be excluded). The outcome measures will be considered mainly at the end of four weeks.

### Search methods for identification of studies

#### Electronic searches

We will conduct a comprehensive literature search to identify all published and unpublished randomised controlled trials with no language restriction. We will search the following electronic databases to identify potential studies:

- Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library) [Appendix 1](#);
- MEDLINE 1966 to present [Appendix 2](#); and
- Embase 1980 to present [Appendix 3](#).

Independent reviewers also will conduct a search for ongoing trials on the ClinicalTrials.gov (clinicaltrials.gov) and World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (apps.who.int/trialsearch). For grey literature we will search in SIGLE (System for Information on Grey Literature in Europe) (www.cf.ac.uk/insrv/eresources/databases/sigle.html) and New York Academic of Medline Library Grey literature collection (www.nyam.org/library/pages/grey\_literature\_report).

### Searching other resources

We will handsearch the published abstracts from the conference proceedings in United European Gastroenterology Week (published in Gut) from 2005 to 2016. We will handsearch references cited in studies found by the above search to identify further relevant trials.

## Data collection and analysis

### Selection of studies

Two independent reviewers will screen the titles and abstracts of papers to assess the eligibility for inclusion in the review. We will document study selection or exclusion and create a list of studies to be included in the analysis. We will resolve any disagreement through discussion or, if required, we will consult a third person (PA). Information on study design, participant characteristics, measurement of FD, adjustment for potential confounders, and estimates of associations will be extracted independently by two reviewers. Discrepancies will be resolved by discussion. We will estimate the agreement level for all steps: title, abstract and full-text screening and data extraction by discussion and reach a consensus.

We will use Endnote to collect and manage citations. Since there may be several published papers with the same result, we will exclude duplicate and similar results and collate all results. Process of study selections will be presented in PRISMA diagram form and we will clarify the characteristics of excluded studies.

### Data extraction and management

Data will be extracted independently using a standard form (which has been piloted by at least one study) by two reviewers to record study characteristics and outcome data. Consensus will be used for inconsistencies between authors. All numeric data from tables, graphs or figures will be confirmed by a second reviewer. In the case of missing data in the included studies, investigators will be contacted (by email, letter and/or fax, phone) to prepare the missing information.

Two review authors will extract the following study characteristics from the included studies:

1. Methods: study design, total duration of study and run-in, number of study centres and location, study setting, withdrawals, date of study.
2. Participants: number of participants, mean age, age range, gender, severity of condition, diagnostic criteria, inclusion criteria, exclusion criteria.
3. Interventions: intervention, comparison, concomitant medications, excluded medications (with or without placebo) and duration of treatment and follow-up time.
4. Outcomes: primary and secondary outcomes specified and collected, with time points reported.

Notes: Funding for trial, notable conflicts of interest of trial authors, name of the author, year of publication, location/country and ethics approval.

### Assessment of risk of bias in included studies

Methodological quality will be assessed independently by at least two review authors according to the *Cochrane Handbook for Systematic Reviews of Interventions* and Cochrane Review guidelines, for each key outcome variable. Review authors will independently assess the risk of bias within each included study based on the following domains with ratings of 'Yes' (low risk of bias); 'No' (high risk of bias) and 'Unclear' (uncertain risk of bias):

- Sequence generation;
- Allocation concealment;
- Blinding (we will collect blinding information by individually identifying the person blinded: single-blind, double-blind and triple-blind);
- Incomplete outcome data;
- Selective outcome reporting.

We will use RevMan software for creation of a 'risk of bias' table. Also, we will create two types of figures with RevMan software for clarifying the risk of bias:

1. A 'Risk of bias' graph, which demonstrates the proportion of studies complying with each of the judgments ('low', 'high' and 'unclear' risk of bias); and
2. A 'Risk of bias' summary, which shows all of the judgments in a cross-tabulation of study by entry.

### Measures of treatment effect

Analysis of dichotomous data will be recorded as risk ratio (RR) and continuous data as mean difference (MD) or standardized mean difference (SMD). Comparison of binary data will be reported as a RR with an associated 95% confidence interval (CI), an absolute risk reduction (ARR) or the number needed to treat to benefit (NNTB) with associated 95% CI, or the Chi<sup>2</sup> test with associated P value. We will collect continuous outcome data (dyspepsia score and quality of life) in three different ways:

1. Unit of measurement or, if unit of measurement cannot be reported (i.e. visual analogue scale), we will consider the data to be unit-less.

2. Measure of central tendency: mean, median, mode.

3. Measure of variance, such as standard deviation, standard error, interquartile range or 95% CI. If raw data are not accessible, we will report the individual study analysis. Continuous data measures will be collected after treatment. Change scores will also be collected (the difference between scores before and after intervention) for comparison. We will undertake meta-analyses only where this is meaningful, i.e. if the treatments, participants and the underlying clinical question are similar enough for pooling to make sense. If the study reported median or inter-quartile range, it is reasonable to assume that the data were skewed. If we suspect the data is skewed, we will exclude studies that do not contain mean and standard deviation; otherwise, median and interquartile range will be used instead of mean and standard deviation, respectively. Where several intervention arms were included in a single study, we will consider only the relevant arms. If two arms of trial were compared to a single placebo group, but reported separately in the text, to avoid double counting in a single meta-analysis, we will halve the placebo number.

### Unit of analysis issues

To reduce the possibility of unit of analysis error, we will take into account the level at which randomisation occurred.

If we face trials with cluster randomizations, we may include each participant as a case in general analysis, but we will mention the detail of such a study in the results and we will conduct a sensitivity analysis to assess the validity of the data. In cross-over trials, we will consider each part of the study as a parallel arm if a washout period was conducted.

### Dealing with missing data

In the first instance, authors will be contacted to provide missing data or clarification of data from included studies (e.g. when a study is identified as an abstract only). Missing data and drop-outs or attrition or both will be assessed for each included study, and the extent to which the results/conclusions of the review could be altered by the missing data will be assessed and discussed.

### Assessment of heterogeneity

Clinical heterogeneity will be assessed by comparing the distribution of important participant factors between trials (e.g. administered dose of drugs, duration of administration of all three drugs), and trial factors (randomization concealment, blinding of outcome assessment, losses to follow-up, treatment type, co-interventions). Within- and between-study heterogeneity will be assessed using Cochran's Q-statistic and the heterogeneity test will be used to assess the null hypothesis that all studies evaluated the

same effect. The effect of heterogeneity is quantified using the  $I^2$  statistic which provides a measure of the degree of inconsistency between studies. If we identify substantial heterogeneity, we will explore it with the prespecified subgroup analysis. We will assess heterogeneity by the  $I^2$  statistic where values of 0% to 40%, 30% to 60%, 50% to 90%, and 75% to 100% will be considered as representing low, moderate, substantial and high level of heterogeneity, respectively.

### Assessment of reporting biases

Funnel plots (estimated differences in treatment effects against their standard error) will be drawn if sufficient (10 or more) studies are found. We will perform a statistical test of the funnel plot using this approach (Egger Test).

### Data synthesis

In order to be able to combine the results, we will consider some possible differences before performing the meta-analysis. For qualitative evidence, we will create a summary table of reviewed studies using the GRADEpro software.

We will provide data regarding study type, comparison, study quality and number of participants involved. We will create a forest plot of the meta-analysis for quantitative synthesis. We will include different comparators (placebo or other active comparators such as H2-receptor antagonists, or prokinetics). However, we will separate studies with different comparators into different subgroups for their analysis. For quantification of calculations, a meta analysis will be performed using RevMan 5 (RevMan 2012). We will use appropriate statistical methods (Curtin 2002) to combine the parallel and cross-over trials. A summary statistic will be calculated for each trial in order to describe the observed intervention effect. For dichotomous outcomes, we will calculate a RR and for continuous data we will calculate a MD. When different instruments have been used, we will use the SMD.

We will calculate a summary (pooled) intervention effect estimate as a weighted average of the intervention effects estimated in the individual studies. We will choose the weights to reflect the amount of information that each study contains. A random-effects model will be used. Meta-regression or sub-group analysis will be used in the case of statistical heterogeneity. We will perform analyses with a fixed-effect model in order to test for heterogeneity. P values less than 0.05 will be considered statistically significant. All statistical tests will be two-sided.

### Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses to reveal any effect that might explain any heterogeneity:

1. People suffering from functional dyspepsia according to different definitions (e.g. Rome III, Rome II criteria) ([ROME criteria](#)).



2. People suffering from functional dyspepsia by category subtype (e.g. epigastric pain type versus postprandial distress type).
3. Treatment duration (less than four weeks versus greater than four weeks).
4. Dose (standard dose versus low dose; table of standard doses).
5. Naive versus treatment-experienced.
6. Geographical location (e.g. Western versus Asian studies).
7. Trial funding sources (industry-sponsored versus nonindustry-sponsored studies).
8. Different control groups (placebo, H2-receptor antagonists, antacids, prokinetics).

### Sensitivity analysis

Sensitivity analyses will be conducted to assess the impact of the study quality. A sensitivity analysis compares studies fulfilling the 'quality' criteria compared to the inclusion of all studies regardless of quality and asks the question, 'Are the findings robust to the decisions made in the process of obtaining them?' This involves the removal of studies that meet certain criteria (e.g. poor-quality, commercial sponsorship, conference abstract) to determine the effect of their inclusion on the overall result. This will be undertaken by including:

1. Only those with low risk of selection bias (associated with sequence generation or allocation concealment);
2. Only those with low risk of performance bias (associated with issues of blinding);
3. Only those with low risk of attrition bias (associated with completeness of data).
4. Fixed-effect versus random-effects models.

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## APPENDICES

### Appendix I. CENTRAL search strategy

1. MeSH descriptor: [Dyspepsia] explode all trees
2. dyspep\* or "NUD" or "FD":ti,ab,kw (Word variations have been searched)
3. indigestion or indigestive:ti,ab,kw (Word variations have been searched)
4. #1 or #2 or #3
5. MeSH descriptor: [Antacids] explode all trees
6. antacid\* or alkalinizing agent\* or antigastralgie agent\*:ti,ab,kw (Word variations have been searched)
7. aluminum or aldrox or algeldrate or alhydrogel or alugel or amphojel or basalgel or brasivil or dialume or nephrox or pepsamer or rocgel:ti,ab,kw (Word variations have been searched)
8. calcium carbonate or aragonite or calcite or calcium milk or Chalk or limestone or marble or vaterite:ti,ab,kw (Word variations have been searched)
9. magnesium or brucite or magnesia:ti,ab,kw (Word variations have been searched)
10. aceglutamide aluminum or alexitol sodium or algicon or Almagate or almagel or alubifar or alugastrin or andursil or attapulgit or bicarbonate or carbex or dihydroxyaluminum sodium carbonate or gaviscon or hydrotalcite or magaldrate or Mylanta or novaluzid or rennie or solugastril or titralac or vangatacite:ti,ab,kw (Word variations have been searched)
11. MeSH descriptor: [Sucralfate] explode all trees
12. (gastro\* or gastric or stomach) and mucosa\* and protect\* and (agent\* or drug\* or medicine\* or medication\*):ti,ab,kw (Word variations have been searched)
13. sucralfate or sulfate or antepsin or carafate or ulcerban or ulcogant or ulsanic:ti,ab,kw (Word variations have been searched)
14. adopilon or alsucral or sulphate or alusac or andapsin or bisma or dolisec or exinol or hexagastron or inpepsa or iselpin or keal or melicide or musin or neciblok or peptonorm or succosa or sucrabest or sucralbene or sucralfin or sucramal or sulcran or sulcrate or treceptan or ufarene or ulcar or ulcekon or ulcerimin or ulcerlmin or ulcertec or ulcogant or ulcyte or ulsaheal or ulsanic or ulsical or ulsidex forte or unival or urbal or venter:ti,ab,kw (Word variations have been searched)
- adopilon or alsucral or sulphate or alusac or andapsin or bisma or dolisec or exinol or hexagastron or inpepsa or iselpin or keal or melicide or musin or neciblok or peptonorm or succosa or sucrabest or sucralbene or sucralfin or sucramal or sulcran or sulcrate or treceptan or ufarene or ulcar or ulcekon or ulcerimin or ulcerlmin or ulcertec or ulcogant or ulcyte or ulsaheal or ulsanic or ulsical or ulsidex forte or unival or urbal or venter:ti,ab,kw (Word variations have been searched)
15. bismuth\*:ti,ab,kw (Word variations have been searched)
16. #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15
17. #4 and #16

## Appendix 2. MEDLINE search strategy

1. exp Dyspepsia/
2. (dyspep\* or "NUD" or "FD").tw,kw.
3. (indigestion or indigestive).tw,kw.
4. or/1-3
5. exp Antacids/
6. (antacid\* or alkalizing agent\* or antigastralgic agent\*).tw,kw.
7. (aluminum or aldrox or algeldrate or alhydrogel or alugel or amphojel or basalgel or brasivil or dialume or nephrox or pepsamer or rocgel).tw,kw.
8. (calcium carbonate or aragonite or calcite or calcium milk or Chalk or limestone or marble or vaterite).tw,kw.
9. (magnesium or brucite or magnesia).tw,kw.
10. (aceglutamide aluminum or alexitol sodium or algicon or Almagate or almagel or alubifar or alugastrin or andursil or attapulgit or bicarbonate or carbex or dihydroxyaluminum sodium carbonate or gaviscon or hydrotalcite or magaldrate or Mylanta or novaluzid or rennie or solugastril or titralac or vangatacite).tw,kw.
11. exp Sucralfate/
12. ((gastro\* or gastric or stomach) and mucosa\* and protect\* and (agent\* or drug\* or medicine\* or medication\*)).tw,kw.
13. (sucralfate or sulfate or antepsin or carafate or ulcerban or ulcogant or ulsanic).tw,kw.

## Appendix 3. EMBASE search strategy

1. exp Dyspepsia/
2. (dyspep\* or "NUD" or "FD").tw,kw.
3. (indigestion or indigestive).tw,kw.
4. or/1-3
5. exp antacid agent/
6. (antacid\* or alkalizing agent\* or antigastralgic agent\*).tw,kw.
7. (aluminum or aldrox or algeldrate or alhydrogel or alugel or amphojel or basalgel or brasivil or dialume or nephrox or pepsamer or rocgel).tw,kw.
8. (calcium carbonate or aragonite or calcite or calcium milk or Chalk or limestone or marble or vaterite).tw,kw.
9. (magnesium or brucite or magnesia).tw,kw.
10. (aceglutamide aluminum or alexitol sodium or algicon or Almagate or almagel or alubifar or alugastrin or andursil or attapulgit or bicarbonate or carbex or dihydroxyaluminum sodium carbonate or gaviscon or hydrotalcite or magaldrate or Mylanta or novaluzid or rennie or solugastril or titralac or vangatacite).tw,kw.
11. exp gastrointestinal mucosa protective agent/
12. ((gastro\* or gastric or stomach) and mucosa\* and protect\* and (agent\* or drug\* or medicine\* or medication\*)).tw,kw.
13. (sucralfate or sulfate or antepsin or carafate or ulcerban or ulcogant or ulsanic).tw,kw.
14. (adopilon or alsucral or sulphate or alusac or andapsin or bisma or dolisec or exinol or hexagastron or inpepsa or iselpin or keal or melicide or musin or neciblok or peptonorm or succosa or sucrahest or sucralbene or sucralfin or sucramal or sulcran or sulcrate or treceptan or ufarene or ulcar or ulcekon or ulcerimin or ulcerlmin or ulcertec orulcogant or ulcyte or ulsaheal or ulsanic or ulsical or ulsidx forte or unival or urbal or venter).tw,kw.
15. exp bismuth/
16. bismuth\*.tw,kw.
17. or/5-16
18. 4 and 17
19. random\*.mp.

20. placebo:.mp.
21. clinical trial:.mp.
22. double-blind:.mp. or blind:.tw.
23. exp health care quality/
24. or/19-23
25. exp animal/ not human/
26. 24 not 25
27. 18 and 24

## Appendix 4. Plain language glossary of terms

Anatomical - relating to bodily structure

Angiogenesis - the formation of different blood vessels

Chronic - long-term

Dyspepsia - indigestion

Dysmotility - a condition in which muscles of the digestive system become impaired and changes in the speed, strength or coordination in the digestive organs occurs

Epigastric - over the stomach

Endoscopy- A procedure in which a hollow tube with a camera on the end is passed through a hollow organ or tube in the body to allow visual inspection or the passage of small surgical instruments

Eradication - destruction

Gastric - stomach related

Gastroduodenal dysmotility

Gastroenteritis - inflammation of the lining of the stomach and intestines

Gastrointestinal - relating to the stomach and intestines

Gastroscopy - an examination of the upper digestive tract using a long, thin, flexible tube containing a camera and a light to view the lining of these organs

H2-receptor antagonists - a type of antacid

Helicobacter pylori - a form of bacteria associated with stomach and duodenal (the first part of the small intestine) ulcers

Hypersensitivity - an excessive or abnormal sensitivity to a substance

Hypochondriasis - the fear of having a serious illness despite not having the condition

Modalities - methods

Motility - a term used to describe the contraction of the muscles that mix and propel contents in the gastrointestinal tract

Neurotoxicity - damage to the brain and nervous system by a poisonous substance

Pathophysiology - the abnormal physical states that accompany a disease

Peptic - relating to digestion

Pepsin - a substance in the stomach that breaks down proteins

Pharmacological - drug related

Polymorphisms - occurring in several different forms

Postprandial - occurring after a meal

Proton pump inhibitors - medications which reduce stomach acid

Psychological - related to a person's mental or emotional state

Satiation - the sensation of having eaten too much

Visceral - the internal organs of the body, specifically those within the chest (as the heart or lungs) or abdomen (as the liver, pancreas or intestines)

## CONTRIBUTIONS OF AUTHORS

Conceiving the protocol: Payman Adibi, Meisam Abdar Isfahani, Najmeh Ahmadi Juzdani, Mojtaba Keikha

Designing the protocol: Payman Adibi, Meisam Abdar Isfahani, Najmeh Ahmadi Juzdani, Mojtaba Keikha, Paul Moayyedi

Coordinating the protocol: Payman Adibi, Meisam Abdar Isfahani, Najmeh Ahmadi Juzdani, Mojtaba Keikha

Designing search strategies: Yuhong Yuan

Writing the protocol: Payman Adibi, Meisam Abdar Isfahani, Najmeh Ahmadi Juzdani, Mojtaba Keikha

Providing general advice on the protocol: Payman Adibi, Neel Sharma, Paul Moayyedi

Performing previous work that was the foundation of the current study: Paul Moayyedi

## DECLARATIONS OF INTEREST

Meisam Abdar Esfahani: none known.

Najme Ahmadi Juzdani: none known.

Mojtaba Keikha: none known.

Peyman Adibi: none known.

Neel Sharma: none known.

Paul Moayyedi: has accepted speaker fees from Shire and Allergan. These companies make drugs for irritable bowel syndrome and ulcerative colitis; PM has had no involvement with pharmaceutical companies that sell drugs to treat any upper gastrointestinal disease. PM's endowed Chair is funded in part by an unrestricted donation given to McMaster University by AstraZeneca Canada.

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